

## TRANSMITTAL LETTER TO THE UNITED STATES

6599 DEB

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

Not yet known

09/403431

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/CH98/00157

22 April 1998

23 April 1997

TITLE OF INVENTION

PROPELLING DEVICE FOR A PISTON IN A CONTAINER CONTAINING A LIQUID MEDICAMENT

APPLICANT(S) FOR DO/EO/US

Daniel Peter and Beat Kindler

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
9. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

## Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.  
A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

- a) Copy of published PCT application (WO 98/47552, published 29 October 1998);
- b) Check

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.101) <b>09/403431</b>	INTERNATIONAL APPLICATION NO. <b>PCT/CH98/00157</b>	ATTORNEY'S DOCKET NUMBER <b>6599 DEB</b>
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20. The following fees are submitted:				<b>CALCULATIONS PTO USE ONLY</b>	
<b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :</b>					
<input checked="" type="checkbox"/>	Search Report has been prepared by the EPO or JPO .....		<b>\$840.00</b>		
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) .....		<b>\$670.00</b>		
<input type="checkbox"/>	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....		<b>\$760.00</b>		
<input type="checkbox"/>	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....		<b>\$970.00</b>		
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....		<b>\$96.00</b>		
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>\$840.00</b>	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				<b>\$130.00</b>	
<b>CLAIMS</b>	<b>NUMBER FILED</b>	<b>NUMBER EXTRA</b>	<b>RATE</b>		
Total claims	20 - 20 =	0	x \$18.00	<b>\$0.00</b>	
Independent claims	3 - 3 =	0	x \$78.00	<b>\$0.00</b>	
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$970.00</b>	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>	
<b>SUBTOTAL =</b>				<b>\$970.00</b>	
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			<input type="checkbox"/>	<b>\$0.00</b>	
<b>TOTAL NATIONAL FEE =</b>				<b>\$970.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$970.00</b>	
				<b>Amount to be: refunded</b>	<b>\$</b>
				<b>charged</b>	<b>\$</b>

- ☒ A check in the amount of **\$970.00** to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \_\_\_\_\_ to cover the above fees.  
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **04-1420** A duplicate copy of this sheet is enclosed.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Dorsey & Whitney LLP  
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Telephone: 612-340-6317  
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SIGNATURE

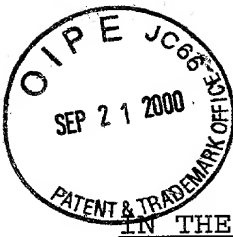
David E. Bruhn

NAME

36,762

REGISTRATION NUMBER

October 22, 1999  
DATE



PCT/PCT Rec'd 21 SEP 2000

Atty Dkt. No. 66624

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Nathan  
Appln. No.: 09/403,443  
Filed: December 20, 1999  
Title: Continuous in vitro  
Evolution of  
Oligonucleotides  
GAU: 1655  
Examiner: A. Chakrabarti

CERTIFICATE OF MAILING

I hereby certify that this paper  
(along with any paper referred to as  
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as first class mail in an envelope  
addressed to: Assistant Commissioner  
for Patents, Washington, D.C. 20231.

9/19/00  
Date

*James P. Kruer*  
Registration No. 35,234  
Attorney for Applicant(s)

AMENDMENT A

Honorable Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

Dear Sir:

This amendment is responsive to an Office Action dated  
March 30, 2000. Please amend the above-identified application  
as follows.

IN THE CLAIMS:

Please cancel claims 1-3.

Please add the following new claims.

4. A method for continuous in vitro evolution of  
oligonucleotides possessing a catalytic activity of ligation,  
splicing, or gap filling, the method comprising:

a) preparing an oligonucleotide mixture of deoxy-oligo-  
nucleotides comprising a plurality of different species of  
oligonucleotides, each species having a different nucleotide  
sequence than the other oligonucleotide sequence in the  
oligonucleotide mixture;

b) contacting the oligonucleotide mixture with a  
substrate oligonucleotide to form functional constructs, the  
functional constructs including only those oligonucleotides

which are effective for acting as substrates for ligation, splicing or gap filling catalytic activity and which are covalently bound to the substrate oligonucleotides;

c) contacting the functional constructs with an amount of RNA polymerase and ribonucleotides effective for forming an RNA transcript;

d) contacting the RNA transcript with an amount of DNA primer, reverse transcriptase, and deoxynucleotides effective for forming an RNA/DNA hybrid;

e) contacting the RNA/DNA hybrid with an Rnase, and

f) repeating steps b through e for a number of times effective for providing an oligonucleotide mixture enriched with oligonucleotides having a catalytic activity of ligation, splicing or gap filling.

5. A method according to claim 4 wherein the substrate oligonucleotide is immobilized on a solid support.

6. A method according to claim 5 wherein heating is conducted after step b at a temperature effective for denaturing oligonucleotides that are not covalently bound to the substrate oligonucleotides.

7. A method according to claim 6 wherein oligonucleotides that are not covalently bound to the substrate oligonucleotides are removed.

8. A kit for continuous in vitro evolution of oligonucleotides possessing a catalytic activity of ligation, splicing, or gap filling, the kit comprising:

an oligonucleotide mixture of deoxy-oligo-nucleotides comprising a plurality of different species of oligonucleotides, each species having a different nucleotide sequence than the other oligonucleotide sequence in the oligonucleotide mixture;

substrate oligonucleotides effective for forming functional constructs, the functional constructs including only those oligonucleotides which are effective for acting as substrates for ligation, splicing or gap filling catalytic activity and which are covalently bound to the substrate oligonucleotides;

an RNA polymerase and ribonucleotides effective for forming an RNA transcript;

a DNA primer, reverse transcriptase, and deoxynucleotides effective for forming an RNA/DNA hybrid; and

an RNase.

#### REMARKS

Upon entry of the present amendment, claims 1-3 have been canceled, claims 4-8 have been added, and claims 4-8 are pending.

#### Rejections Over the Cited References

Neither of the cited references describes a process or kit for the continuous in vitro evolution of oligonucleotides possessing a catalytic activity of ligation, splicing, or gap filling. Further, neither reference describes or suggests a process where the catalytic activity comprises a functional promoter or a process where the catalytic activity of the evolving sequence attaches the substrate, including the promoter, to themselves.

#### U.S. Patent No. 5,807,718 to Joyce et al.

The '718 patent does not describe or suggest a continuous method for producing oligonucleotides having a catalytic activity of ligation, splicing, or gap filling having all of the elements as now claimed and required under 35 USC 102.

1. The method of the '718 patent is not continuous.

The '718 patent describes a multiple step process that requires an addition of a biotinylated primer after each cycle and requires significant technician intervention to complete. More specifically, the '718 patent describes the preparation of a double stranded DNA pool by using PCR with a biotinylated DNA primer (column 24, lines 43-45). Biotinylated DNA strands of DNA are immobilized on a streptavidin matrix (column 24, lines 50-53), and DNAs that undergo  $Pb^{2+}$ -dependent self-cleavage are recovered (column 24, lines 55-56) by requiring a technician to add a buffer that contains  $Pb^{2+}$ . Further PCR amplification of recovered DNAs is conducted (column 24, lines 58-59). Since the promoter in the '718 process is not expressed, a new oligonucleotide construct that includes a functional promoter must be added after every cycle. Hence, the '718 process is not continuous. The process of the present invention is continuous as during the process a new oligonucleotide construct including a functional promoter is created by the activity of nucleotide attachment.

2. The '718 patent does not describe a method for producing oligonucleotides with ligation, splicing or gap filling catalytic activity.

The '718 patent is directed to a method for the amplification of DNAs that cleave target RNA phosphodiesterases (Fig. 1, column 24, lines 41-42). The '718 patent deals only with the catalytic activity of cleavage, while the present invention as claimed is directed to the catalytic activity of attachment (ligation, splicing or gap filling).

3. The '718 patent does not describe the use of RNA polymerase, reverse transcriptase or Rnase.

The '718 patent describes a standard PCR amplification where any DNA that hybridizes to a primer is replicated. The '718 patent does not describe the formation of a functional

construct as claimed, forming an RNA transcript from the construct, using a reverse transcriptase to form an RNA/DNA hybrid, use of an RNase to remove RNA, or the repeating of these steps.

4. The `718 patent teaches away from the present invention.

One of ordinary skill in the art would be taught by the `718 patent to screen for cleavage reactions. This type of cleavage activity is the type of catalytic activity that should be avoided by the present invention, where only nucleotides for attachment are selected.

U.S. Patent No. 5,130,238 to Malek et al.

The `238 patent does not describe a method or kit for the continuous evolution of oligonucleotides having a catalytic activity of ligation, splicing or gap filling as claimed. The `238 patent describes amplification processes where promoter must be added after each cycle. Hence, the `238 patent is not continuous as claimed.

#### SUPPLEMENTAL IDS

Submitted herewith is a Supplemental IDS that cites references found in searching of corresponding PCT applications.


#### Conclusion

In view of the above amendments and remarks, Applicant respectfully requests that the pending claims be passed to issue.

The Commissioner is hereby authorized to charge any additional fees which may be required in this application to Deposit Account No. 06-1135.

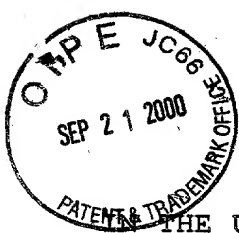
Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By   
James P. Krueger  
Registration No. 35,234

Date: Sept. 19, 2000

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PATENT APPLICATION

Attorney Docket No. 66624

Date: September 19, 2000

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: NATHAN

Application No.: 09/403,443

Filed: December 20, 1999

For: CONTINUOUS IN VITRO EVOLUTION  
OF OLIGONUCLEOTIDES

Group Art Unit: 1655

Examiner: A. Chakrabarti

## CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on this date.

9/19/00

Date Registration No. 35,234  
Attorney for Applicant

Commissioner of Patents and Trademarks  
ATTENTION: Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

(X) Information Disclosure Statement, IDS 1449; 3 PCT publications and 7 references; Check \$240 filing IDS.

## Fee Calculation For Claims As Amended

	As Amended	Previously Paid For	Present Extra	Rate	Additional Fee
Independent Claims	2	3	** = 0	x \$ 78.00	= \$ 0
Total Claims	5	20	* = 0	x \$ 18.00	= \$ 0
Fee for Multiply Dependent Claims				\$260.00	\$ 0
** At least 3			Total Additional Fee		\$ 0
* At least 20					

( ) Small Entity Fee (reduced by half)

\$

( ) A check in the amount of \$ is attached.

( ) Charge \$ to Deposit Account No. 06-1135.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required in this application under 37 C.F.R. §§1.16-1.17 during its entire pendency, or credit any overpayment, to Deposit Account No. 06-1135. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 06-1135. A duplicate copy of this sheet is enclosed.

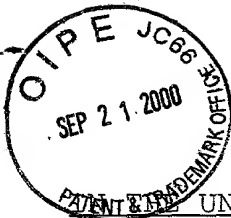
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ATTY DKT. NO. 66624

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Nathan )  
Appln. No.: 09/403,433 )  
Filed: December 20, 1999 )  
Title: CONTINUOUS IN VITRO )  
EVOLUTION OF )  
OLIGONUCLEOTIDES )  
GAU: 1632 )  
Examiner: A. Chakrabarti )

CERTIFICATE OF MAILING

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addressed to: Assistant Commissioner  
for Patents, Washington, D.C. 20231.

9/19/00 *James P. Kim*  
Date Registration No. 34,234  
Attorney for Applicant(s)

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

Dear Sir:

Pursuant to the duty of disclosure under 37 C.F.R. 1.56,  
submitted herewith is a Information Disclosure Statement and  
PTO Form 1499 along with copies of all materials cited  
therein.

Foreign Patent Documents

<u>Document No.</u>	<u>Date</u>
WO 98/08974	Mar. 5, 1998
WO 96/40723	Dec. 19, 1996
WO 96/17086	June 6, 1996

Search Report

<u>Document No.</u>	<u>Country</u>	<u>Date</u>
PCT/IL 98/00186	PCT	Sept. 24, 1998

Other References

Breaker et al., "A DNA enzyme that cleaves RNA,"  
Chemistry and Biology, Vol. 1, No. 4, 1994, pp. 223-229.

Wright et al., "Continuous In Vitro Evolution of  
Catalytic RNA," 1950, XP-002074722.

Wright et al., "Continuous In Vitro Evolution of Catalytic RNA," Science, Vol. 276, pp. 614-617, April 25, 1997.

Famulok et al., "In Vitro Selection of Specific Ligand-binding Nucleic Acids," Angew. Chem. Int. Ed. Engl., pp. 979-988, 1992.

Herranz et al., "In vitro selection of active hairpin ribozymes by sequential RNA-Catalyzed cleavage and ligation reactions," Genes & Development, Vol. 6, pp. 129-134, 1992.

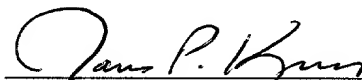
Kumar et al., "Artificial evolution and natural ribozymes," The FASEB Journal, Vol. 9, pp. 1183-1195, September 1995.

Breaker et al., "A DNA enzyme with Mg<sup>2+</sup>-dependent RNA phosphoesterase activity," Chemistry & Biology, Vol. 2, No. 10, pp. 655-660, 1995.

Enclosed herewith is a check in the amount of \$240.00 in accordance with 37 CFR 1.97.

The Commissioner is hereby authorized to charge any additional fees which may be required in this application to Deposit Account No. 06-1135.

Respectfully submitted,



James P. Krueger  
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Date: Sept. 19, 2000

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09/403431

420 Rec'd PCT/PTO 22 OCT 1999

Docket: 6599

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Daniel Peter and Beat Kindler

Serial No.: Not yet known

Filing Date: Herewith

Title: Propelling Device for a Piston in a Container Containing a Liquid Medicament

**Preliminary Amendment**

Assistant Commissioner for Patents  
Box PCT  
Washington D.C. 20231

Dear Sir:

Please preliminarily amend the above-identified application as follows:

**In the Claims**

Please amend claims 1-15 as follows:

1. (Amended) An apparatus for administering a liquid medicament, [consisting of at least] comprising a housing [(1; G)], a piston [(K)], a container[ (A)] and a propelling device, said propelling device comprising:
- (a) a base element [(1)];

Express Mail mailing label number EL115447733 US

Date of Deposit October 22, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington D.C. 20231

Brian Ballard

Name

Signature

(b) a first shifting stage [(10)] being shiftable relative to said base element [(1)], said first shifting stage, on shifting, advances said piston [(K)] in said container [(A)] resulting in said liquid medicament being dispensed from said container [(A)] in a metered manner[,] and

(c) at least a second shifting stage [(20)] being shiftable relative to said base element [(1)] as well as relative to said first shifting stage [(10)] in said advance direction of said piston [(K)] and slaving said first shifting stage [(10)] in its shifting movement in the advance direction of said piston [(K)],

(d) said first and said second shifting stages [(10, 20)], when seen in said advance direction of said piston [(K)], overlap at least in part,

[characterized in that] wherein said propelling device and said container [(A)] are accommodated and fixed in place in the [common] housing [(1; G)], that said piston [(K)] is held in said container [(A)] and said first shifting stage [(10)] is connected to said piston [(K)] only by exerting contact pressure on said piston [(K)].

2. (Amended) The propelling device [as set forth in] of claim 1, characterized in that said first and said second shifting stages [(10, 20), intermeshing] are operably connected by a male thread [(15)] and a female thread [(25)], forming a first spindle drive, the rotational movement of which causes said first shifting stage [(10)] to shift.

3. (Amended) The propelling device [as set forth in the preceding claim] of claim 2, [characterized in that] wherein said second shifting stage [(20)] shifts as the driven member of a second spindle drive [(20, 30; 20, 6)].

4. (Amended) The propelling device [as set forth in the preceding claim] of claim 3, [characterized in that] wherein said second shifting stage [(20) may be both] is movably slaved [in rotation and shifted] by a drive member [(30)] of said second spindle drive [(20, 30)].
5. (Amended) The propelling device [as set forth in the preceding claim] of claim 4, [characterized in that a] wherein the thread [(26)] of said second shifting stage [(20) with which said second shifting stage engages said drive member (30) of said second spindle drive (20, 30)] and the thread [(15)] of said first shifting stage [(10)] have the same hand.
6. (Amended) The propelling device [as set forth in] of claim 3, [characterized in that] wherein said second shifting stage [(20)] is rotary driven and forms, together with a reaction member [(6)] which is non-rotatable relative to said base element [(1 ; G)], said second spindle drive [(20, 6)].
7. (Amended) The propelling device [as set forth in] of claim 3, [characterized in that] wherein said first shifting stage [(10)] is rotary driven and forms, together with said second shifting stage [(20)] which is non-rotatable relative to said base element [(1 ; G)], said first spindle drive.
8. (Amended) The propelling device [as set forth in any of the claims 3 to 7] of claim 1, [characterized in that] wherein the axis of rotation of said two spindle drives are in alignment.
9. (Amended) The propelling device [as set forth in any of the claims 1 to 7] of claim 2, [characterized in that] wherein said first shifting stage [(10)] and a shifting axis of said second shifting stage [(20)] are [spaced away] parallel to each other.
10. (Amended) The propelling device [as set forth in] of claim 3, [characterized in that] wherein said first shifting stage [(10)] is rotationally driven by said drive member [(30)] of said second spindle drive [(20, 30)] via a spur gear unit [(38a, 38b, 38c)].

11. (Amended) The propelling device [as set forth in one or several of the preceding claims] of claim 10, [characterized in that] wherein one of [either] said first shifting stage [(10) or] and said second shifting stage [(20)] is prevented from rotating relative to said base element [(1 ; G)] by an anti-rotation lock [(40; 40a)].

12. (Amended) The propelling device [as set forth in the preceding claim characterized in that] of claim 11, wherein said anti-rotation lock is formed by a slipper [(40),] having at least one sliding surface area relative to said base element [(1 ; G)] and at least one sliding surface area relative to said first shifting stage [(10)], said sliding surface areas permitting shifting and preventing a rotation of said first shifting stage [(10)] relative to said base element [(1 : G)].

13. (Amended) The propelling device [as set forth in the preceding claim] of claim 12, [characterized in that] wherein said slipper [(40)] is jointly shifted together with said second shifting stage [(20)].

14. (Amended) The propelling device [as set forth in any of the claims 11 to] of claim 13, c[haracterized in that] wherein said anti-rotation lock [(40)] comprises a sleeve body [(43)] substantially surrounding [components of] said propelling device [, thereby protecting them from dirt].

15. (Amended) A portable medicament administrating device comprising at least:

- (a) a housing [(1 ; G)];
- (b) a reservoir [(A)] for a liquid medicament to be administered;
- (c) a piston [(K)] which, by advancing, dispenses in a metered manner said liquid medicament to be administered from said reservoir [(A)]; and

(d) a propelling device [(10, 20) as set forth in at least one of the preceding claims] for advancing said piston [(K)].

Please add claims 16-20 as follows:

16. An apparatus for administering a substance, comprising a housing, a piston, a container and a propelling device, the propelling device comprising:

a base element;

a first shifting stage shiftable relative to said base element; and

a second shifting stage shiftable relative to said base element and to said first shifting stage and slaving said first shifting stage, wherein said propelling device and the container and piston are operably coupled to the housing and a portion of said first shifting stage is in contact with the piston.

17. The apparatus according to claim 16, wherein said first and said second shifting stages are operably coupled by respective complementary threaded portions to form a first spindle drive, the rotational movement of which causes said first shifting stage to shift.

18. The apparatus according to claim 17, further comprising a second spindle drive, wherein said second shifting stage shifts as the driven member of the second spindle drive.

19. The apparatus according to claim 18, wherein said second shifting stage is substantially slaved in both rotation and shift by a drive member of said second spindle drive.

20. The apparatus according to claim 19, wherein said first and second shifting stages overlap in part.

Remarks

The above amendments have been made in order to correct informalities and conform the claims to U.S. practice, and to protect embodiments of the present invention.

No additional claim fees should be generated by the above amendments, but the Office is hereby authorized to charge any additional fees associated with this communication to Deposit Acct. 04-1420.

The Examiner is invited to telephone the undersigned if doing so would help advance the prosecution of the application.

Respectfully submitted,

Date:

October 22, 1999

By

David E. Bruhn

David E. Bruhn

Registration No. 36,762

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Minneapolis, Minnesota 55402-1498

Telephone: 612-340-6317

Attorneys for Applicant

*Amend*

Propelling device for a piston in a container containing a liquid medicament

The invention relates to a propelling device for a piston in a container containing a liquid medicament.

For administering medicaments in fluid form, more particularly in liquid form, for example insulin, portable injection and/or infusion devices find application. The liquid medicament is dispensed and administered finely metered from a fluid container by means of a piston. These devices find wide application as pumping devices and manually- actuated pens in insulin treatment. An injection pen is known, for example, from WO 93/16740. One example of such a portable infusion device is the H-TRON® plus insulin pump made by Disetronic Medical Systems AG. The user normally carries the device about with him all the time, for example at work or when on vacation. To ensure best possible freedom from an external supply, on the one hand, and freedom of movement, on the other, the device is designed to accommodate as much liquid medicament as possible without being bulky. This requirement for a compact design also exists basically in the medical field; thus also as regards stationary devices and systems.

The object of the invention is to provide a propelling device for a piston in a container containing a liquid medicament which is compact and thus particularly suited as the propelling device for a portable medicament administering device.

This object is achieved by the subject matter of claim 1.

Just like known propelling devices, for example, the H-TRON® plus pump made by Disetronic Medical Systems AG known from EP 0143895 or the injection pen known from WO 93/16740, the propelling device in accordance with the present invention comprises a shifting stage shiftably mounted in or on a base element which, on shifting, advances a piston in a container containing a liquid medicament and thereby

medicament from the container. Metering the amount of fluid to be dispensed occurs by setting the path length of the advance movement of the piston at the shifting stage.

In addition to the first shifting stage, at least a second shifting stage is provided which is shiftable in the advance direction of the piston relative to the base element and also relative to the first shifting stage, either manually or motor-driven, and carries the first shifting stage along when shifted in the advance direction of the piston. Due to the multistage operation of the propelling device, the maximum path length by which the piston can be advanced is split up into several increments, namely one increment per shifting stage. The at least two shifting stages are arranged overlapping at least in part in their starting positions. By splitting up the maximum shifting path length into several increments by cascading the propelling device, the overall length of the fluid container and the propelling device, as measured in the advance direction of the piston, is reduced. The shifting stages form preferably a telescopic drive.

Telescopic drives are known from WO 94/15660 and WO 97/00091 which are inserted in a medicament container open at the back end, and are secured to the container, whereby a drive spindle is power-rotated. Two shifting stages, each surrounding the drive spindle, run on and co-axially to the drive spindle. The outer one of these two shifting stages is prevented from rotating, in the case of WO 97/00091, with the aid of an anti-rotation lock to be extended with the outer shifting stage. By rotating the drive spindle, the middle shifting stage running thereon and the outer, non-rotatable shifting stage running on the middle shifting stage are advanced in the container to a container orifice. The piston for dispelling the liquid medicament is secured to the front end of the outer shifting stage.

In accordance with the invention, no fixed connection exists between the container, including piston, and the propelling device, instead the propelling device and the container, including piston, are each separately accommodated in a common housing so that either the container with the piston contained therein or the propelling device or both can be simply exchanged, since a connection of the propelling device to the piston and/or to the container does not first of all have to be released. This facilitates in particular replacing the container,

for example, after all its contents have been administered. The propelling device can remain in the housing since it is not involved.

Preferably the propelling device too, is accommodated in the housing for being replaced new. The housing can directly form the cited base element. In a likewise preferred embodiment, the base element forms with the shifting stages accommodated therein and a motor drive, preferably mounted therein, an easily replaceable drive module secured in the housing. The first shifting stage of the propelling device comprises with the piston merely one contacting connection, i.e. it loosely contacts the piston or comes into contact with it only to advance it. The physical separation also renders it, in principle, possible to use the same propelling device for various forms of containers and also in conjunction with various types of pistons.

The shifting stages involved are preferably rigid components, linearly shiftable along one spatial axis only, although, of course, it is just as possible to employ flexible stages to approximate the fluid container.

How the several shifting stages are disposed with respect to each other is dictated by the individual application. Thus, in an arrangement corresponding to one preferred exemplary embodiment, the shifting stages disposed shiftable with respect to the base element are arranged so that their sliding axis, which are simultaneously the longitudinal axes, are in alignment. In its starting position, the one shifting stage thus surrounds the other like a sleeve. Arranging the shifting stages nested also has the advantage of a minimum extension transverse to the advance direction, this being used to advantage in both injection pens and in pumping devices.

If room is available alongside the fluid container, as is the case for example in the H-TRON<sup>®</sup> plus pump, as already cited, at least one shifting stage may be advantageously arranged there. While the axis, along which the one shifting stage is shifted in the direction of advancement of the piston, is located in the extension of the piston advance direction, the shifting axis of the other shifting stage is distanced parallel thereto.

The shifting stages are shifted preferably by spindle drives with respect to the base element and also relative to each other. Mating of the spindle drive threads is preferably arranged as near as possible to the piston. As a separate spindle drive is used for shifting each shifting stage with respect to the other and, finally, with respect to the base element, a rotational movement initiated, manually or powered, in the propelling device at a point is translated into a continually cumulative shifting movement. Using spindle drives permits one to precisely set the shifting distance. In addition, a spindle drive is also able to carry out the function of a mounting fixture between the individual shifting stages.

In accordance with one example embodiment, one of the two shifting stages is fixedly connected to a rotary drive. The two spindle drives, connected in series, comprise opposing threads. The total distance traveled per rotation of the rotary-driven shifting stage then always equals the sum of the shifting distances traveled by both shifting stages thus coupled. Thus, when thread pitches are the same, for example, a shifting travel is achieved which corresponds to twice the thread pitch of each individual shifting stage.

In accordance with another embodiment of the invention, the threads of two spindle drives connected in series have the same hand. The one shifting stage is advanced by the spindle drive member which rotary drives it or is carried along in the rotational movement. As far as it is shifted, it simply slaves the next shifting stage in its movement. As far as being simply slaved in rotation by the spindle drive member, its own rotational movement generates a forced shifting movement of the subsequent shifting stage prevented from being slaved into rotation by the an anti-rotation lock. This kind of spindle drive cascading permits a particularly precise setting of the shifting travel of the propelling device.

Although the invention primarily finds application in portable infusion and/or injection devices it may also be used to advantage in stationary systems.

The invention will now be explained by way of preferred embodiments with reference to the drawings in which:

- Fig. 1 is a plan view of a first example embodiment of a propelling device in accordance with the invention,
- Fig. 2 is a longitudinal section C-C taken through Fig. 1,
- Fig. 3 is a longitudinal section D-D taken through Fig. 1,
- Fig. 4 is the longitudinal section as shown in Fig. 2, but with the propelling device in its fully extended position,
- Fig. 5 is the longitudinal section as shown in Fig. 3, but with the propelling device in its fully extended position,
- Fig. 6 is an overall view in perspective of the propelling device as shown in Figs. 1-5
- Fig. 7 is an illustration of the drive sleeve of the propelling device as shown in Figs. 1 to 6,
- Fig. 8 is an illustration of the feed nut of the propelling device as shown in Figs. 1 to 6,
- Fig. 9 is an illustration of the feed screw of the propelling device as shown in Figs. 1 to 6,
- Fig. 10 is an illustration of the anti-rotation lock of the propelling device as shown in Figs. 1 to 6,
- Fig. 11 is a longitudinal section through a second example embodiment of a propelling device in accordance with the invention,
- Fig. 12 is another longitudinal section through the propelling device as shown in Fig. 11,
- Fig. 13 is a longitudinal section through a third example embodiment of a propelling device in accordance with the invention,
- Fig. 14 is another longitudinal section through the propelling device as shown in Fig. 13,
- Fig. 15 is a longitudinal section through a fourth example embodiment of a propelling device in accordance with the invention,
- Fig. 16 is another longitudinal section through the propelling device as shown in Fig. 15,
- Fig. 17 is a longitudinal section through a fifth example embodiment of a propelling device in accordance with the invention,

- Fig. 18 is another longitudinal section through the propelling device as shown in Fig. 17,
- Fig. 19 is a plan view of a sixth example embodiment of a propelling device in accordance with the invention,
- Fig. 20 is a longitudinal section D-D taken through the propelling device as shown in Fig. 19,
- Fig. 21 is a longitudinal section E-E taken through the propelling device as shown in Fig. 19,
- Fig. 22 is an overall view in perspective of the propelling device as shown in the Figs. 19 to 22,
- Fig. 23 is an illustration of an injection device including a propelling device in accordance with the invention
- Fig. 24 is an illustration of an infusion device including a propelling device in accordance with the invention
- Fig. 25 is an illustration of a seventh example embodiment of a propelling device in accordance with the invention, and
- Fig. 26 is an illustration of the anti-rotation lock of the propelling device as shown in Fig. 25.

In the plan view of a propelling device as shown in Fig. 1, the locations of the longitudinal sections illustrated in Figs. 2 and 3 are marked.

As its main components, the propelling device comprises a base element 1, two shifting stages 10 and 20, linearly shiftable with respect to the base element 1, an axially fixed rotary drive member 30, rotationally mounted in the base element 1, and a motor 4, rotationally driving the rotary drive member 30. The first shifting stage 10 is configured as a threaded rod with a male thread 15. The second shifting stage 20 is a threaded sleeve having a female thread 25 and a male thread 26. The rotary drive member 30 is likewise cylindrically tubular and will be termed drive sleeve in the following, it comprising a female thread 36 in a head portion and a slaving gearwheel 22 in a footing portion.

The slaving gearwheel 33 meshes with a gearwheel 5 located on the shaft of the motor 4. The threaded rod 10 and the threaded sleeve 20 form by their threads 15 and 25 a first spindle drive. The threaded sleeve 20 and the drive sleeve 30 form by their threads 26 and 36 a second spindle drive. The two sleeves 20 and 30 surround the threaded rod 10 concentrically about a common longitudinal centerline simultaneously pointing in the advance direction of the propelling device. In this advance direction, the propelling device, in itself being advanced, advances a piston accommodated in a reservoir or container containing a liquid medicament, for example in the form of a prefabricated syringe body, by the threaded rod 10, as the most proximal or first shifting stage advancing the piston by means of a proximal flange 11 urging the piston in the direction of the orifice of the container to thus dispel fluid from the container. In this arrangement, the base element 1 locates the propelling device with respect to the container. The base element 1 may be secured to a frame or in a housing, or itself form the frame or housing.

In the base element 1, the drive sleeve 30 is rotatively mounted, as well as located axially and radially, in a bearing position 3a, preferably a plain bearing for rotation about the longitudinal centerline of the propelling device, simultaneously forming the axis of rotation thereof. A radial bearing position 3b for the drive sleeve 30 is located in the upper portion of the base element 1. The threaded sleeve 20 is supported in the drive sleeve 30 by the second spindle drive formed between the threads 26 and 36, i.e. the threaded sleeve 20 is shiftable via the second spindle drive with respect to the drive sleeve 30 and is also freely rotatable in the second spindle drive.

The threaded rod 10 is prevented from rotating with respect to the base element 1. This anti-rotation lock is achieved by means of an anti-rotation fork 40, which is linearly shiftable with respect to the threaded rod 10, but is not rotatable and which itself is locked against rotating in the base element 1, and is slidingly guided along the longitudinal centerline of the propelling device.

Advancement of the threaded rod 10 thus occurs as follows:

The rotative movement of the motor is transmitted via the spur reduction gearing 5, 33 to the drive sleeve 30. The rotative movement of the drive sleeve 30 is transmitted via the

second spindle drive formed between the threads 36 and 26 to the threaded sleeve 20. Depending on the frictional forces acting on the threaded sleeve 20, the threaded sleeve 20 is either slaved in the rotative movement or advanced along its axis of rotation by the spindle drive comprising the threads 26, 36. The movement of the threaded sleeve 20 may also be a compounded telescoping/rotative movement. When only shifting of the threaded sleeve 20 is involved, it simply slaves the threaded rod 10 in this movement. When compounded slave rotation of the threaded sleeve 20 is involved, the rotative movement of the threaded sleeve 20 produces via the second spindle drive formed by the threads 15 and 25 an advance movement of the threaded rod 10 with respect to the threaded sleeve 20 due to the anti-rotation lock of the threaded rod 10. To achieve this movement characteristic, the threads 26 and 15, i.e. the threads via which each of the two shifting stages 10 and 20 are driven have the same hand.

Referring now to Figs. 2 and 3, the propelling device is illustrated in a position in which it is partly extended from a starting position in the base element 1. In the starting position, the two nested shifting stages 10 and 20 are accommodated in a cavity of the base element 1. In this starting position, each of the two shifting stages 10 and 20 is in contact with the bottom of the cavity by its rear face contacting a bottoming surface area 2.

Referring now to Figs. 4 and 5, illustrated is the propelling device in the same sections as shown in Figs. 2 and 3, but here in the fully extended position. In this position, the propelling device is also illustrated in an overall view in perspective in Fig. 6.

The proximal end position of the threaded rod 10 in the threaded sleeve 20 is dictated by a pair of stops 17, 27 and the most proximal end position of the threaded sleeve 20 in the drive sleeve 30 is dictated by a pair of stops 28, 38 (Fig. 5). Each of the stops 27 and 38 is formed as a circumferential shoulder protruding radially inwards from the inner circumferential surface areas of the nut/sleeve 20 and 30 respectively, whilst the corresponding counter-stops 17 and 27 are formed by thickened annular portions of the threaded rod 10 and threaded sleeve 20 respectively.

A third pair of stops 8, 44 prevents the anti-rotation fork 40 from dropping out of the propelling device. The fork 40 may also be fixed to the threaded sleeve 20. The stop 8 is formed by shoulders 7 protruding inwards in the direction of the shifting axis at the proximal end of the cavity of the base element 1. The anti-rotation fork 40 comprises at its distal end corresponding, counterhook-type protuberances 44, jutting radially outwards.

Referring now to Fig. 7, it illustrates a longitudinal section of the drive sleeve 30. This essentially comprises a simple cylindrically-tubular base body 31, configured thickened in the footing portion 32 in order for better guidance of the drive sleeve 30, so that the outer shell surface area of the footing portion 32 slides in the right cylindrical cavity of the base element 1 on rotation of the drive sleeve 30, and represents an additional means of radially stabilizing the system with respect to the bearing 3. The slaving gearwheel 33 is a simple spur gear formed by a rim gear shoulder radially surrounding the shell surface area of the drive sleeve 30. At its proximal end, the drive sleeve 30 is provided within a shoulder portion 34 protruding radially inwards with a thread 36, which may be a fine thread, a multiple coarse pitch thread or even a regulating thread. The face 38 of the shoulder portion 34, facing the footing portion 32, forms the stop for the threaded sleeve 20.

Referring now to Fig. 8, illustrated is the threaded sleeve 20 which likewise essentially comprises a simple cylindrically-tubular base body 21. Starting from the most proximal end of the base body 21, the threaded sleeve 20 is provided over by far the majority of its length with a thread 26 which runs in the thread 36 of the drive sleeve 30. The distal portion 22 of the threaded sleeve 20 is a simple annular cylinder, the outer diameter of which is somewhat larger than the outer diameter of the portion having the thread 26. Due to this thickening, the counter-stop 28 is formed for the stop 38 of the drive sleeve 30. The footing portion 22 is slide-guided in the drive sleeve 30, it featuring furthermore a circumferential recess at 23, this recess 23 serving to seat a sealing ring. At the proximal end, the threaded sleeve 20 comprises a shoulder portion 24 protruding radially inwards. In the shoulder portion 24, the thread 35 is configured (the same applying to it as what was said about thread 36). The face of the shoulder 24 facing the footing portion 22 serves as the stop 27 for the threaded rod 10.

Fig. 9 illustrates the threaded rod 10, likewise formed by a right cylindrical base body. A simple right cylindrical footing portion 12 is itself slightly thickened with respect to the substantially longer threaded portion, the footing portion 12 also serving as a sliding guide in shifting the threaded rod 10 in the threaded sleeve 20. Seated in a circumferential annular container 13 in the footing portion 12 is a sealing ring in the fitted condition. The portion with the thread 15 has two opposing flats 14. At its proximal end, the threaded rod 10 is faced with a blind hole 16 to which the flange 11 is bolted. In cooperation with the anti-rotation fork 40, the flat 34 prevents the threaded rod 10 rotating with respect to the base element 1.

Fig. 10 shows finally the anti-rotation fork 40. It is a sleeve open at one end and closed off at the other end by a disk 41, the sleeve being provided with slots over its entire length, two slots being evident in the example embodiment, owing to which or to the strip-shaped longitudinal receiving portions it has the form of two-pronged fork. The disk 41 is provided with a port 42 which is penetrated by the threaded rod 10 in the fitted condition. This port 42 is defined by two circumferential flats joined by the annular cylinder surface areas. The threaded rod 10 is thus axially slide-guided in the region of its thread 15 and of its two guide flats 14 in the port 42 but is prevented from rotating relative thereto by the anti-rotation fork 40. The two axial projections 43 are snugly slide-guided in the base element 1 so that the anti-rotation fork 40 is itself unable to rotate with respect to the base element 1, it instead merely permitted a longitudinal sliding action. It is in this way that rotation of the threaded rod 10 with respect to the base element 1 is prevented. As already mentioned, counterhook-shaped projections 44 at the distal end of the anti-rotation fork 40 prevent the anti-rotation fork 40 from dropping out of the base element 1.

Referring now to Figs. 11 to 18, shown are four alternative example embodiments of propelling devices in accordance with the invention. In these examples too, as in the first example embodiment, the straight lines, along which the shifting stages 10 and 20 are telescoped, are in alignment. Figs. 19 to 22 show a sixth example embodiment in which the first and the second shifting stages are shifted on straight lines distances parallel to each other. In the following, components comparable to those of the first example embodiment are assigned the same reference numerals since they fulfill the same function as those of the

former. Reference is always made to the detailed explanations of the first example embodiment in supplementing the following description.

Unlike in the first example embodiment, in the following example embodiments to be described no free rotation of a shifting stage is permitted.

Each rotational movement introduced by a shifting stage is inevitably translated into a corresponding shifting movement of this shifting stage.

In the example embodiment of Figs. 11 and 12, the rotational movement of the motor 4 is transmitted via the rim gear 5, 33 directly to the threaded sleeve 20, "direct" in this context meaning that rotation of the slaving gearwheel 33 with respect to the threaded sleeve 20 is not possible. The threaded sleeve 20 is shifted closely slide-guided in a longitudinal direction in the slaving gearwheel 33 non-rotationally. In this example embodiment, the threaded rod 10 is formed cylindrically-tubular with a circumferential male thread 15 and an inner circumferential surface area in which an anti-rotation lock 40 is slide-guided. Via their threads, the threaded rod 10 and the threaded sleeve 20 form - as in the first example embodiment - a first spindle drive. The second spindle drive is formed by the threaded sleeve 20 and the base element 1, said base element being provided with a thread 36 in a proximal shoulder portion 6 protruding radially inwards in the direction of the threaded sleeve 20. Via the threads 26 and 36, the threaded sleeve 20 and the shoulder portion 6 of the base element 1 form the second spindle drive. As viewed cross-sectionally, the threaded sleeve 20 forms a circular ring with two outer flats for the longitudinal guidance, and the thread 26 on the two circular segment sides for the rotary drive by the slaving gearwheel 33.

In the example embodiment as shown in Figs. 11 and 12, the anti-rotation lock 40 is guided in the inner cavity of the threaded rod 10 and prevents its rotation with respect to the base element. The anti-rotation lock 40 comprises a footing portion 43 which is slide-guided in the base element locked against rotating. Protruding from the footing portion 43 is a guide rod 42 which totally passes through the threaded rod 10 in the starting position of the propelling device. The guide rod 42 is formed so that it prevents rotation of the first shifting

stage 10 with respect to the base element whilst permitting shifting. The second shifting stage 20 is seated on the footing portion 43 of the anti-rotation lock 40, connected thereto so that it is freely rotational with respect to the footing portion 43, on the one hand, but slaving the anti-rotation lock 40 in its own shifting movement, on the other, thus including the first shifting stage 10 in the shifting movement.

The rotation of the threaded sleeve 20 slaved by the slaving gearwheel 33 results in the threaded sleeve 20 being shifted by means of the second spindle drive in the advance direction V or in the opposite direction, the base element 1 acting as the direct reaction member of the second spindle drive, i.e. the threaded sleeve 20 is simultaneously the drive member and driven member of the second spindle drive. It is furthermore also the drive member of the first spindle drive, the driven member of which is the threaded sleeve 10. The thread 26 leading to shifting of the threaded sleeve 20 and the corresponding thread 15 of the threaded sleeve 10 have the opposite hand. Every rotational movement of the threaded sleeve 20 always produces shifting of the threaded sleeve 10 due to a relative rotation.

Figs. 13 and 14 illustrate a propelling device which functions comparable to that as shown in Figs. 11 and 12. As regards the matching features, reference is made more particularly to the latter, but always supplementary to the explanations of the first example embodiment.

The propelling device as shown in Figs. 13 and 14 comprises likewise two spindle drives. However, in this example embodiment, the first shifting stage 10 nests the second shifting stage 20 although still termed a feed screw. The first spindle drive is formed by a female thread 15 of the threaded rod 10 and a corresponding male thread of the threaded sleeve 20. An anti-rotation lock 40 prevents rotation of the threaded rod 10 with respect to the base element 1. The anti-rotation lock 40 is comparable to the anti-rotation fork of the first example embodiment. The rotary drive of the threaded sleeve 20 is achieved by means of an axially fixed drive sleeve 30, rotationally mounted in the base element 1. In its footing portion, this drive sleeve 30 is rigidly connected to a slaving gearwheel which meshes with a gearwheel on the shaft of the motor 4. The threaded sleeve 20 is prevented from rotating in the drive sleeve 30, resulting in a transfer of the rotational movement from the drive sleeve 30 to the threaded sleeve 20 while permitting longitudinal slide-guided shifting. The

drive sleeve 30 is furthermore centrally penetrated by a feed screw 6. The feed screw 6 is rigidly connected to the base element 1. In this way, the rotational movement of the drive sleeve 30 is translated into a rotational movement of the threaded sleeve 20 and by means of the feed screw 6 into a shifting movement of the threaded sleeve 20.

Referring now to Figs. 15 and 16, illustrated is a further propelling device in which, however, the threaded rod 10 is directly driven in rotation and the threaded sleeve 20 is prevented from any rotation with respect to the base element 1. The rotary drive of the drive sleeve 30 occurs like in the example shown in Figs. 13 and 14, except that within the drive sleeve 30 a rod-shaped rotary drive member 50 is provided non-rotationally connected thereto for the first threaded rod 10. This rotary drive/slaving rod 50 protrudes from a cover secured to the distal face end of the drive sleeve 30 in the advance direction and into the threaded rod 10. The rotary drive rod 50 is configured itself multi-stage, i.e. in the example embodiment two-stage corresponding to the number of movable shifting stages - like a telescope - following extension of the threaded rod 10. The threaded sleeve 20 is prevented from rotating with respect to the base element 1 by an anti-rotation lock 40a provided as sliding surface area directly on the base element 1. This is why any rotation of the drive sleeve 30 is always translated into a shifting movement of the threaded sleeve 20. Due to the non-rotational connection, any rotation of the drive sleeve 30 results in the same rotation of the rotary drive rod 50 and thus of the threaded sleeve 10.

The example embodiment shown in Figs. 17 and 18 substantially corresponds to that as of Figs. 15 and 16, the differences in design being already apparent from Figs. 17 and 18.

Figs. 19 to 22 illustrate a sixth example embodiment. In this example embodiment, the first and second shifting stages are moved along two straight lines parallel to each other, i.e. the shifting axles of the first and the second spindle drives are spaced away parallel to each other. Included in the plan view in Fig. 19 are the locations of the two longitudinal sections shown in Figs. 20 and 21.

Also in this sixth example embodiment, components having the same functions as those of previous example embodiments are given the same reference numerals.

Advancement of the most-proximal first shifting stage 10 is again achieved by a rotary drive of a drive stage 30 which in this example embodiment is devised as a simple spindle. The spindle 30 is rotationally mounted in the base element 1, but prevented from any other movement with respect to the base element 1. The axis of rotation of the spindle 30 runs in the advance direction V1 and V2 of the shifting stages 10 and 20. The spindle 30 is itself rotary driven by a motor 4 via spur gears 5, 33. Seated on the spindle 30 is a first sleeve body 20a of the second shifting stage 20. The second shifting stage 20 is U-shaped. The sleeve body 20a forms one leg of the U and a second sleeve body 20b, spaced away from the other parallel thereto, forms the other leg of the U. The two sleeve bodies 20a and 20b protrude perpendicularly from a connecting web 20c, said sleeve bodies forming therewith as the cover a housing of the second shifting stage 20. In the base element 1, the sleeve body 20a and the connecting web 20c are movably slide-guided along the axis of rotation of the spindle 30, and prevented from rotating. In the second sleeve body 20b, the first shifting stage 10, again configured as a feed screw, is shifted in and contrary to the advance direction of the piston and shiftingly rotated around the longitudinal centerline of the second sleeve body 20b which coincides with its own longitudinal centerline.

Rotation of the spindle 30 causes the second shifting stage 20 to be forcibly shifted along the axis of rotation of the spindle via the pairing of the threads 26, 36. Seated on the spindle 30, non-rotationally with respect to the spindle 30 but axially shiftable, is a spur gear 38a. Slide-guiding and non-rotational shifting is formed by flats on the circumference of the spindle 30 and corresponding companion flats on the spur gear 38a. The spur gear 38a is accommodated in the housing 20a-c of the second shifting stage 20 so that it is slaved in the shifting movement of the latter while being freely rotational with respect to the housing of the shifting stage 20. Rotationally mounted in the housing of the shifting stage 20 are, furthermore, a second gearwheel 38b meshing with the spur gear 38a as well as a third spur gear 38c meshing with the spur gear 38b. The three gearwheels 38a, 38b and 38c form a spur gear unit for rotary drive of a slaving rod 50, protruding perpendicularly from the gearwheel 38c, for the threaded rod 10. The slaving rod 50 protrudes into the cylindrically-tubular threaded rod 10 and is non-rotationally slide-guided. It slaves the threaded rod 10 in its own rotation compulsorily and with zero clearance. Like in the aforementioned example

embodiments, rotation of the threaded rod 10 is translated into a shifting movement of the threaded rod 10 by means of a first spindle drive formed by the pairing of the threads 15, 25.

Fig. 23 shows a so-called pen as used in particular for insulin injection. Accommodated in the housing G of the injection pen is a syringe body A comprising a piston K and containing a liquid medicament. The piston is shiftable in the direction of a syringe body orifice in an advance direction V, dispelling on its advancement a precisely metered amount of fluid from the syringe body A via a needle hub into and through a needle N. The piston K is held in the syringe body A, i.e. it is removed together with the syringe body A and may be replaced by a new syringe body with a new piston. The base element 1 serves, together with a dispensing and actuator knob 4, to mount the propelling device, is accommodated independent of the container A in the housing G, and is fixed in its position relative to the container A and the piston K. However, with its proximal edge, the base element 1 serves to locate the syringe body A. Accordingly, screwing open the housing G results in a proximal and a distal housing sleeve, the syringe body A being accommodated in the proximal housing half and the propelling device in the distal housing half. When screwed together, the base element 1 is forced against the distal edge of the syringe body so as to seat the syringe body A non-shiftable in a longitudinal direction in the housing G.

Advancement of the piston K is caused by extension of a threaded rod 10 which, on being extended, urges against the distal end of the piston to advance the piston K in the syringe body A. The threaded rod 10 forms the first shifting stage of a telescopic drive. The second shifting stage is formed by a threaded sleeve 20 in which the threaded rod 10 runs by means of a first spindle drive. The threaded sleeve 20 is itself nested in a drive sleeve 30 with which it forms a second spindle drive for extending and retracting it in and against the advance direction V. The drive sleeve 30 is rotationally mounted in the housing 1. The drive sleeve 30 is manually turned with respect to the housing G by means of the dispensing and actuator knob 4 around the longitudinal centerline of the propelling device 10, 20, 30, pointing in the advance direction V, for setting the dose of insulin to be administered, and is then advanced together with the threaded rod 10 and the threaded sleeve 20 along the longitudinal axis. After injection or after actuation of a reset knob, the

feed nut is then returned into its starting position ready for the next injection, due to a spring F thereby being compressed.

Dispensing and manually actuating the injection pen occurs as in known pens, reference being made in this respect, for example, to the description of such an injection pen in WO 93/16740. However, contrary to known injection pens, a propelling device in accordance with the invention is used for the piston K of the pen as shown in Fig. 23. The propelling device of this example application corresponding the first example embodiment.

Fig. 24 illustrates a portable infusion device, more particularly for insulin treatment, including a motor-powered propelling device, for instance, the propelling device as shown in the Figs. 1 to 10. The base element 1 - including the drive sleeve 30, two shifting stages 10 and 20 and the anti-rotation fork 40 - is fixed in place in the pump housing G by, among other things, being mutually shaped accordingly.

To facilitate its replacement, the syringe body A including the piston K retained therein can be simply inserted in and removed from the housing G in the example as shown in Fig. 23. In other words, free of any connection first needing to be released. When replacing the syringe body A, the propelling device can remain in the housing G or be replaced independent of the syringe body A. However, as already discussed with reference to the example embodiment as shown in Fig. 23, the base element 1 serves as a stopper, i.e. for locating the syringe body A lengthwise. The syringe body A can be moved to and fro in an insertion shaft of the housing G until this stop, it thereby being guided lengthwise. After insertion, it is locked in place to prevent it from being advanced in the shaft by means of the locking means to be secured to the housing G.

In extending from the most distal position of the propelling device as shown in Fig. 24, the threaded rod 10 urges the piston K into the syringe body A in the direction V towards the syringe body orifice which in the example embodiment is, still at this time, sealed off tight by a diaphragm. The propelling device is powered by the motor 4 via a spur gear unit 5a to 5f as well as 33. For further details as to the propelling device, reference is made particularly to the example embodiment as shown in Figs. 1 to 10. However, instead of this,

the other propelling devices as described above may be likewise employed. Thus, for example, the propelling device as shown in Figs. 19 to 22 could be ideally installed in the space available alongside the syringe body A and the stages of the propelling device.

Figs. 25 and 26 illustrate a seventh example embodiment of the invention having a propelling device which is substantially the same as that of the first example embodiment. Fig. 25 is an illustration of the propelling device in an overall view in perspective, in a view from above with the two entered sections A-A and B-B and parts of these two sections. Fig. 26 is an illustration of an anti-rotation lock 40 in an overall view in perspective as viewed from the rear and in the two sections A-A and B-B as entered. Also evident from Fig. 26 is a slaving element 41a, applied to the anti-rotation lock 40, which is a further development of the anti-rotation lock of the first example embodiment.

However, the anti-rotation lock 40 of the seventh example embodiment is not formed by an anti-rotation fork with penetratable linear guiding slots, instead the anti-rotation lock 40 surrounds the part of the propelling device extensible from the base element 1 with the exception of the extended part of the first shifting stage 10. The anti-rotation lock 40 of the seventh example embodiment is configured as a closed sleeve body providing soilage protection, it preferably being made as a ceramic component. Instead of penetration slots, this sleeve body 43 comprises two groove-shaped recesses 43a oriented in the longitudinal direction of the sleeve body 43, the linear guiding means of the base element 1 engaging each of these recesses for linear guidance of the anti-rotation lock 40. This linear guidance as such is comparable to that of the first example embodiment. In this example embodiment, two linear recesses 43a are provided ending in the proximal circumferential edge of the sleeve body 43. In principle, even a single recess would suffice, however, also more than two recesses 43a may be provided.

Inserted in the sleeve body 43 is a slaving element 41a, screwed to the disk 41 forming the bottom of the sleeve. As best evident from Fig. 26, the slaving element 41a is a partly annular component, semi-circular in the example embodiment, the outer circumferential surface areas are partly in close contact with the inner circumferential surface area of the sleeve body 43 for the purpose of positioning the screw holes. The slaving element 41a forms a cuff for the second shifting stage 20 and serves to slave the anti-rotation lock 40 in

the movement of the second shifting stage 20. For this purpose, the slaving element 41a engages a circumferential recess in the outer shell surface area of the second shifting stage 20 by a flange 41b protruding radially inwards from an inner circumferential surface area. The anti-rotation lock 40 is locked from shifting in both the extending direction and the retraction direction at the second shifting stage 20 without, however, obstructing the rotational movement of the second shifting stage 20.

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Amend

What is claimed is:

1. An apparatus for administering a liquid medicament, consisting of at least a housing (1; G), a piston (K), a container (A) and a propelling device, said propelling device comprising:
  - a) a base element (1)
  - b) a first shifting stage (10) being shiftable relative to said base element (1), said first shifting stage, on shifting, advances said piston (K) in said container (A) resulting in said liquid medicament being dispensed from said container (A) in a metered manner, and
  - c) at least a second shifting stage (20) being shiftable relative to said base element (1) as well as relative to said first shifting stage (10) in said advance direction of said piston (K) and slaving said first shifting stage (10) in its shifting movement in the advance direction of said piston (K),
  - d) said first and said second shifting stages (10, 20), when seen in said advance direction of said piston (K), overlap at least in part,

**characterized in that** said propelling device and said container (A) are accommodated and fixed in place in the common housing (1; G), that said piston (K) is held in said container (A) and said first shifting stage (10) is connected to said piston (K) only by exerting contact pressure on said piston (K).
2. The propelling device as set forth in claim 1, characterized in that said first and said second shifting stages (10, 20), intermeshing by a male thread (15) and a female thread (25), form a first spindle drive, the rotational movement of which causes said first shifting stage (10) to shift.
3. The propelling device as set forth in the preceding claim, characterized in that said second shifting stage (20) shifts as the driven member of a second spindle drive (20, 30; 20, 6).

4. The propelling device as set forth in the preceding claim, characterized in that said second shifting stage (20) may be both slaved in rotation and shifted by a drive member (30) of said second spindle drive (20, 30).
5. The propelling device as set forth in the preceding claim, characterized in that a thread (26) of said second shifting stage (20) with which said second shifting stage engages said drive member (30) of said second spindle drive (20, 30) and the thread (15) of said first shifting stage (10) have the same hand.
6. The propelling device as set forth in claim 3, characterized in that said second shifting stage (20) is rotary driven and forms, together with a reaction member (6) which is non-rotatable relative to said base element (1 ; G), said second spindle drive (20, 6).
7. The propelling device as set forth in claim 3, characterized in that said first shifting stage (10) is rotary driven and forms, together with said second shifting stage (20) which is non-rotatable relative to said base element (1 ; G), said first spindle drive.
8. The propelling device as set forth in any of the claims 3 to 7, characterized in that the axis of rotation of said two spindle drives are in alignment.
9. The propelling device as set forth in any of the claims 1 to 7, characterized in that said first shifting stage (10) and a shifting axis of said second shifting stage (20) are spaced away parallel to each other.
10. The propelling device as set forth in claim 3, characterized in that said first shifting stage (10) is rotationally driven by said drive member (30) of said second spindle drive (20, 30) via a spur gear unit (38a, 38b, 38c).

11. The propelling device as set forth in one or several of the preceding claims, characterized in that either said first shifting stage (10) or said second shifting stage (20) is prevented from rotating relative to said base element (1 ; G) by an anti-rotation lock (40; 40a).

12. The propelling device as set forth in the preceding claim, characterized in that said anti-rotation lock is formed by a slipper (40), having at least one sliding surface area relative to said base element (1 ; G) and at least one sliding surface area relative to said first shifting stage (10), said sliding surface areas permitting shifting and preventing a rotation of said first shifting stage (10) relative to said base element (1 : G).

13. The propelling device as set forth in the preceding claim, characterized in that said slipper (40) is jointly shifted together with said second shifting stage (20).

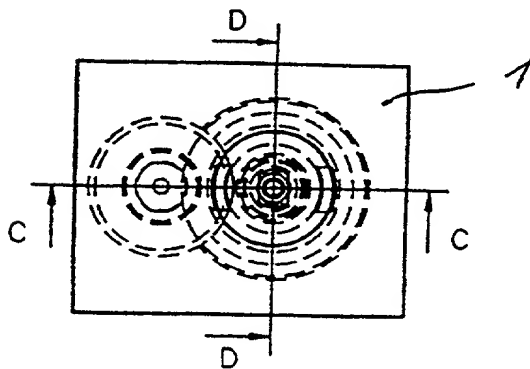
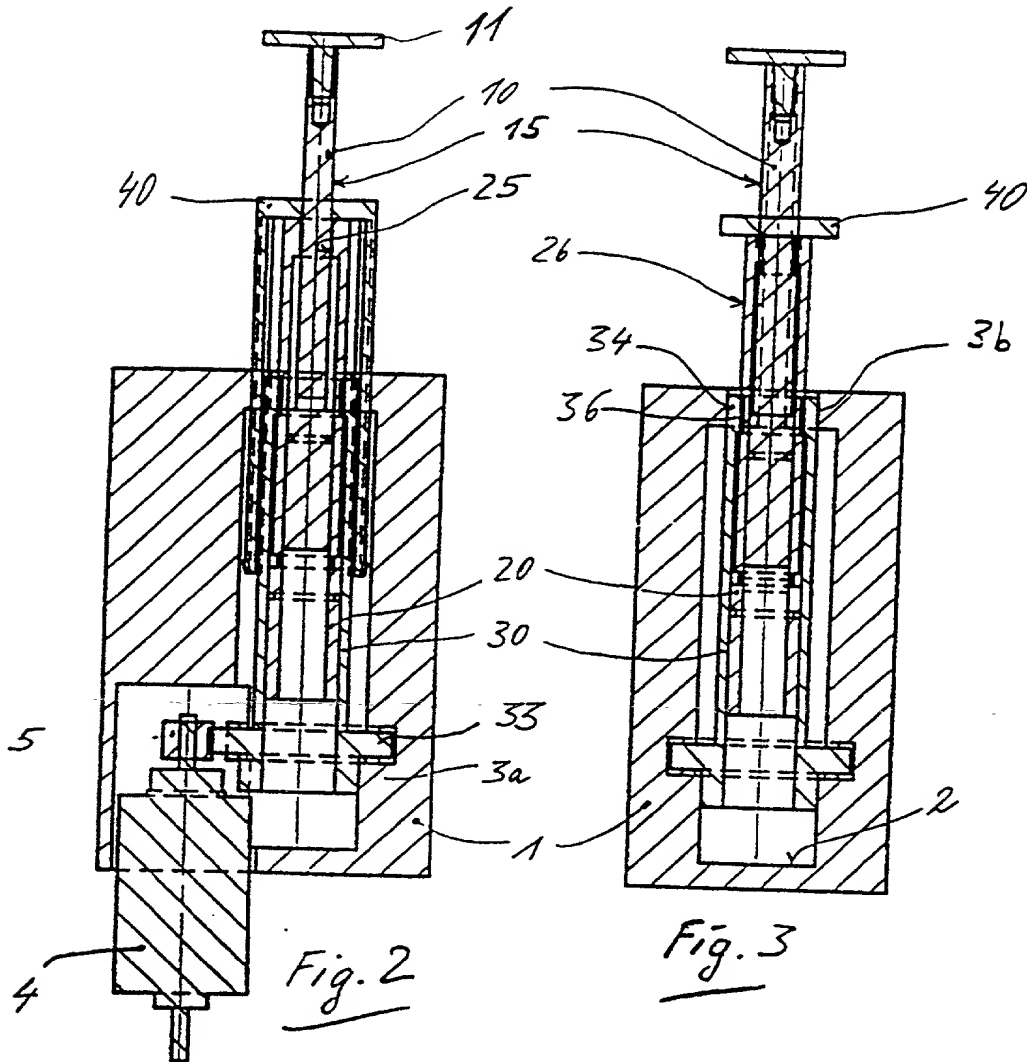
14. The propelling device as set forth in any of the claims 11 to 13, characterized in that said anti-rotation lock (40) comprises a sleeve body (43) surrounding components of said propelling device, thereby protecting them from dirt.

15. A portable medicament administrating device comprising at least

- a) a housing (1 ; G)
- b) a reservoir (A) for a liquid medicament to be administered
- c) a piston (K) which, by advancing, dispenses in a metered manner said liquid medicament to be administered from said reservoir (A) and
- d) a propelling device (10, 20) as set forth in at least one of the preceding claims for advancing said piston (K).

Sectional View C-C

Sectional View D-D



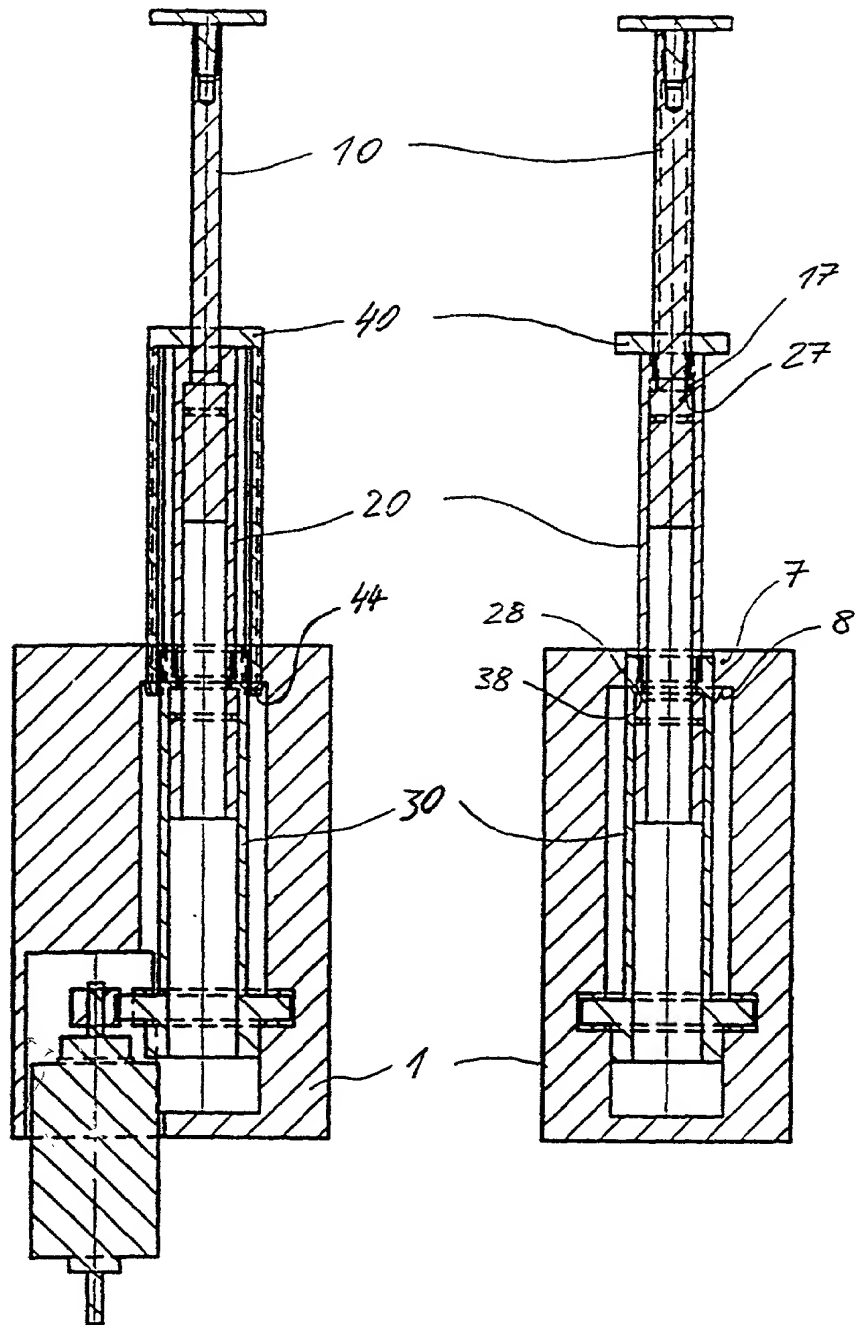
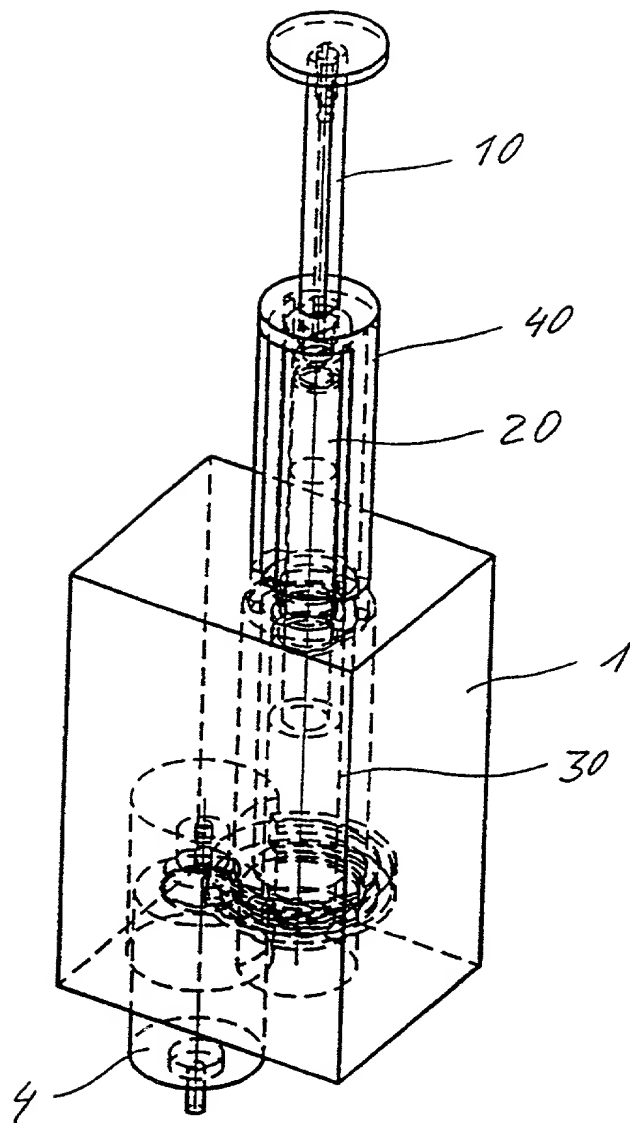
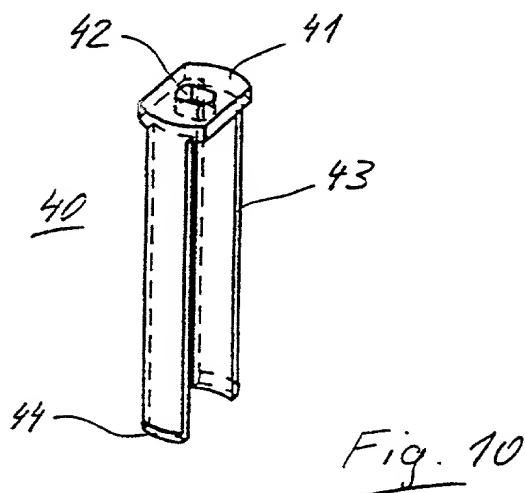
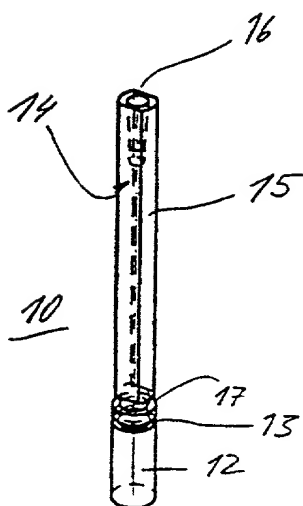
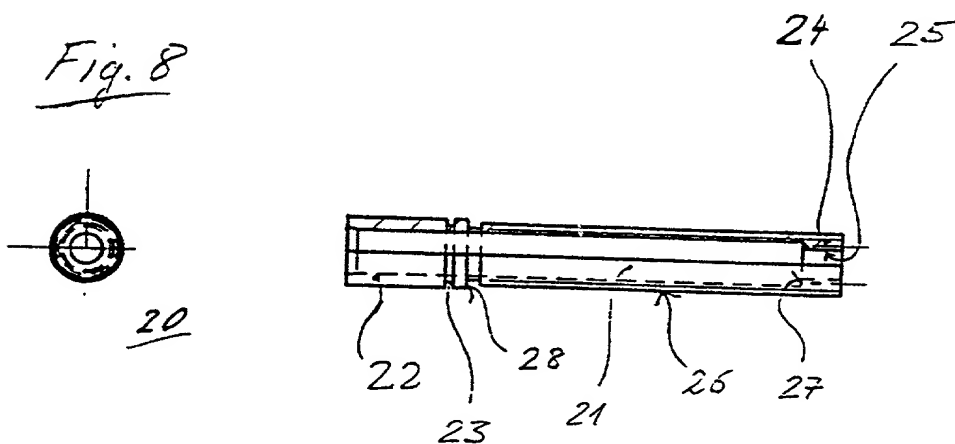
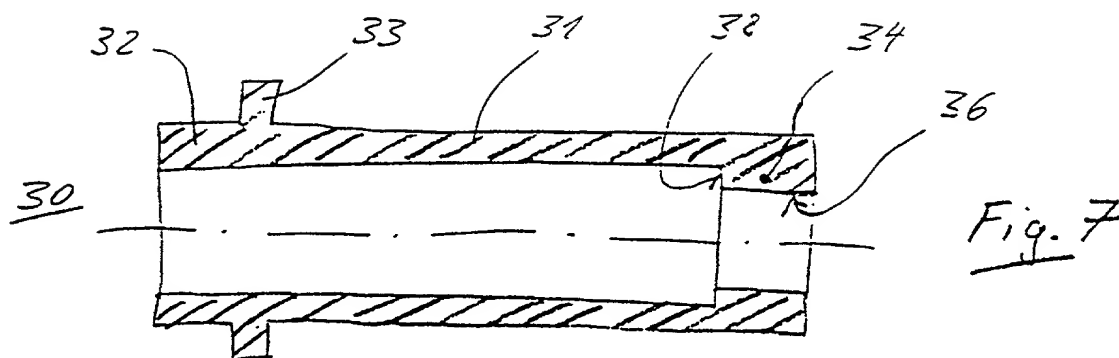


Fig. 4

Fig. 5

Fig. 6



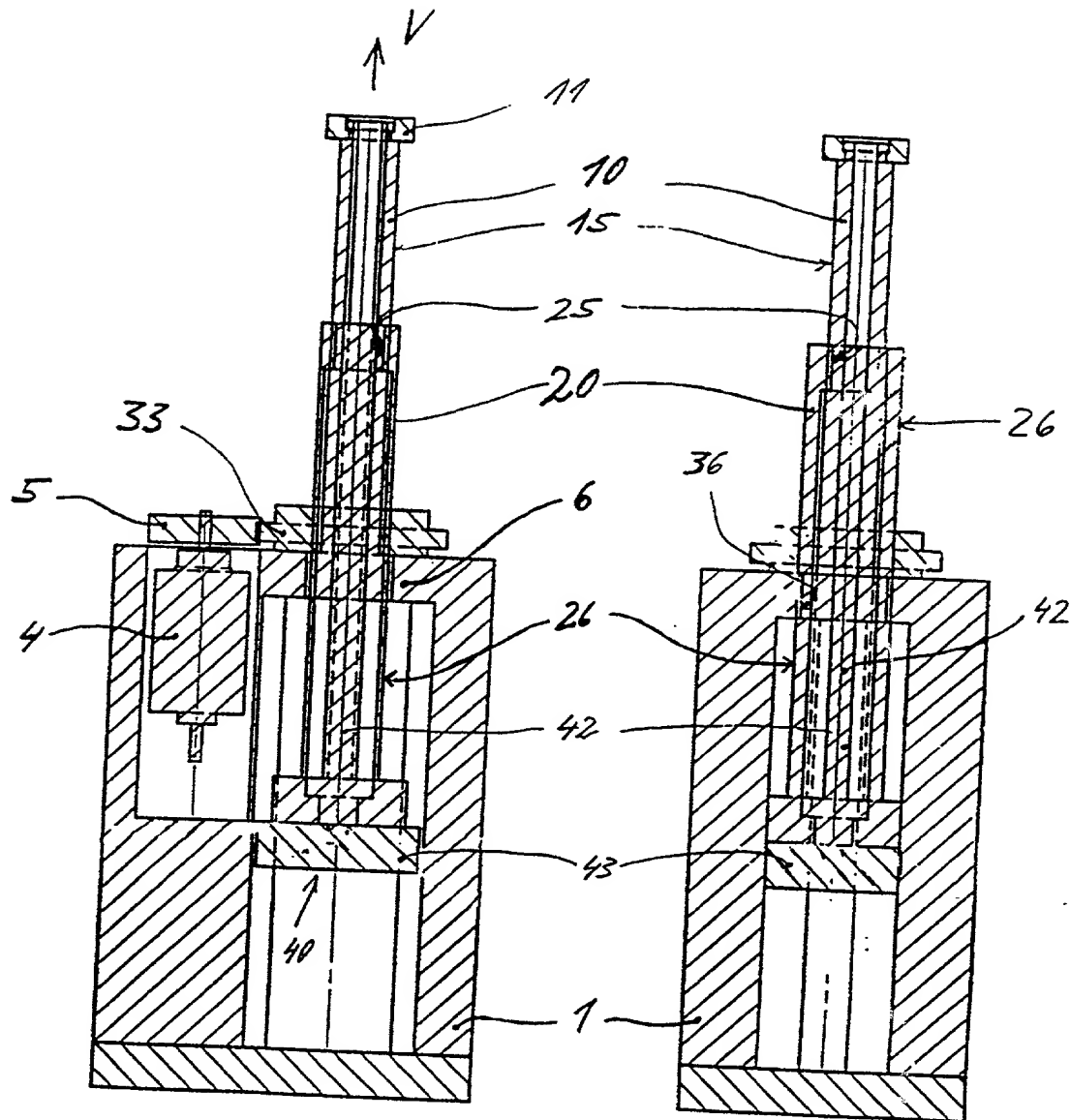
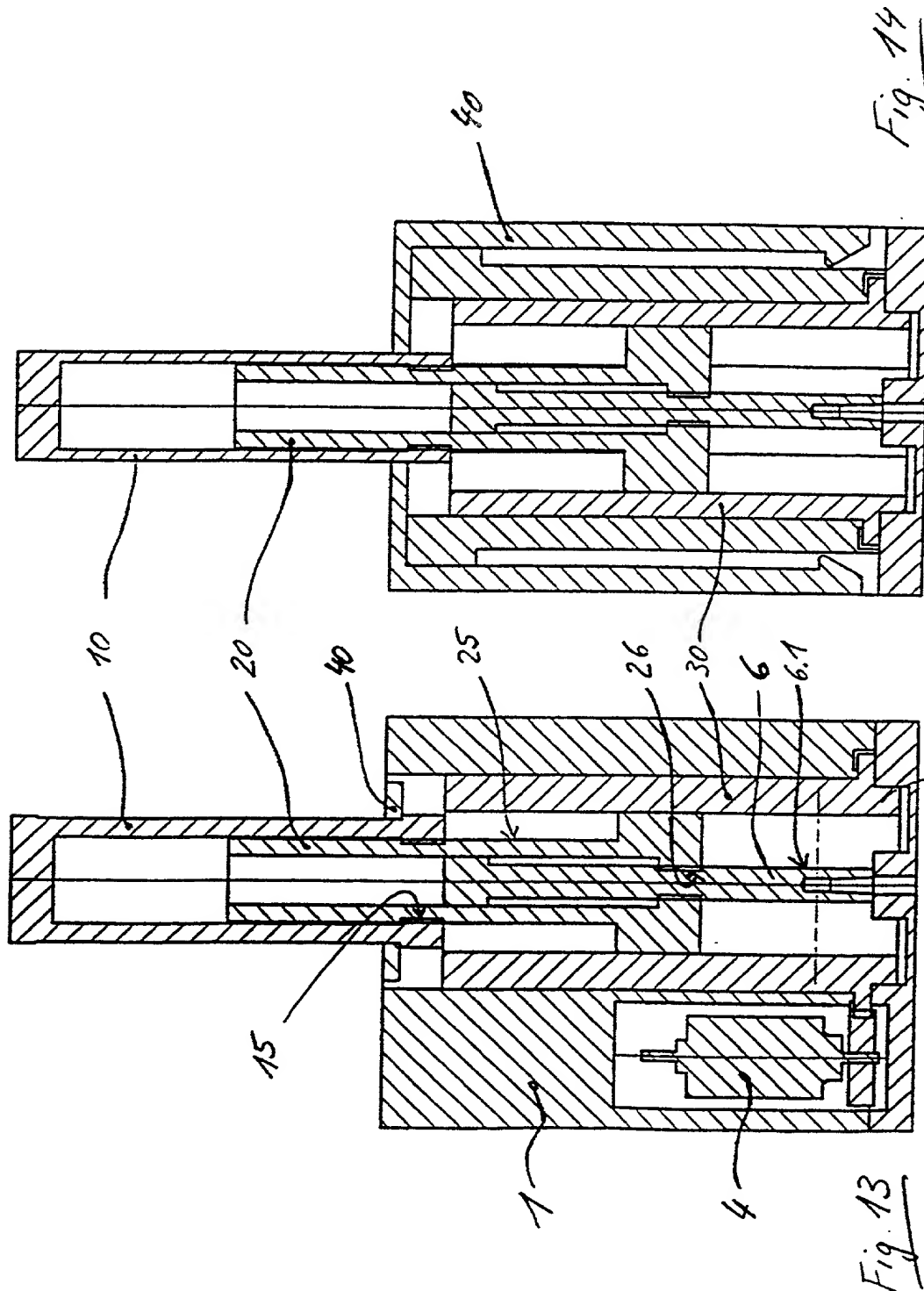
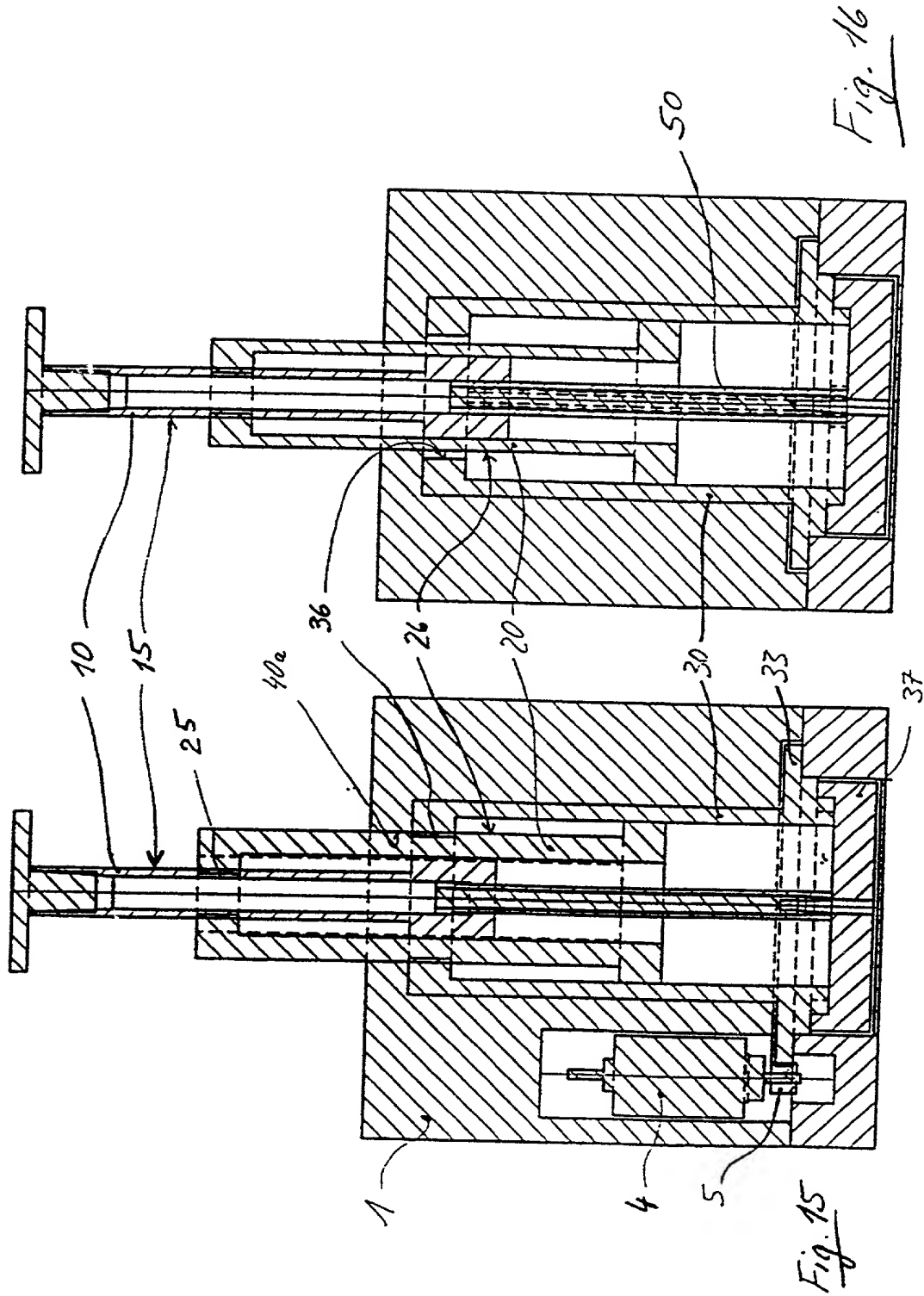


Fig. 11

Fig. 12





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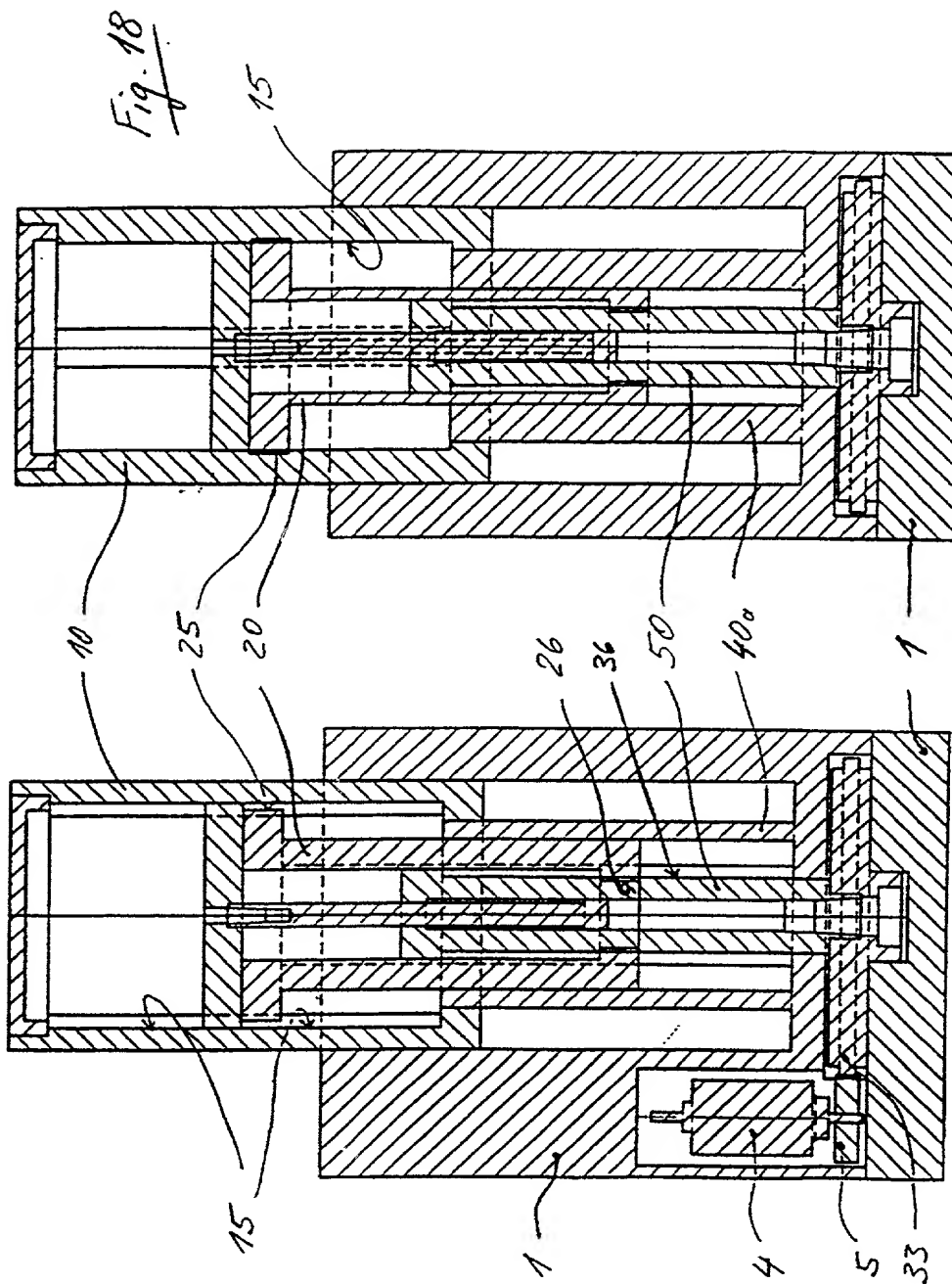


Fig. 18

Fig. 17

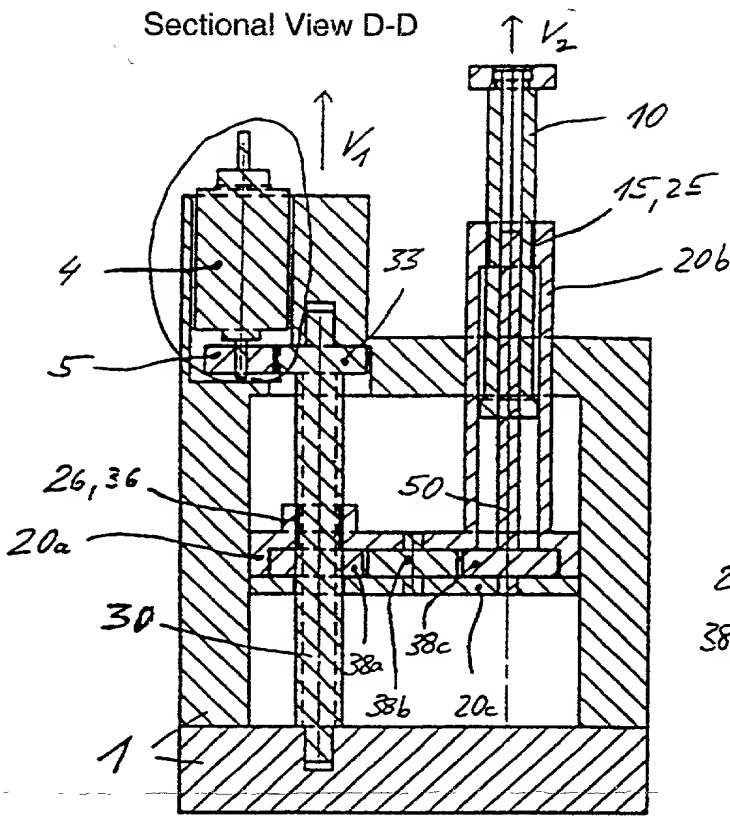


Fig. 20

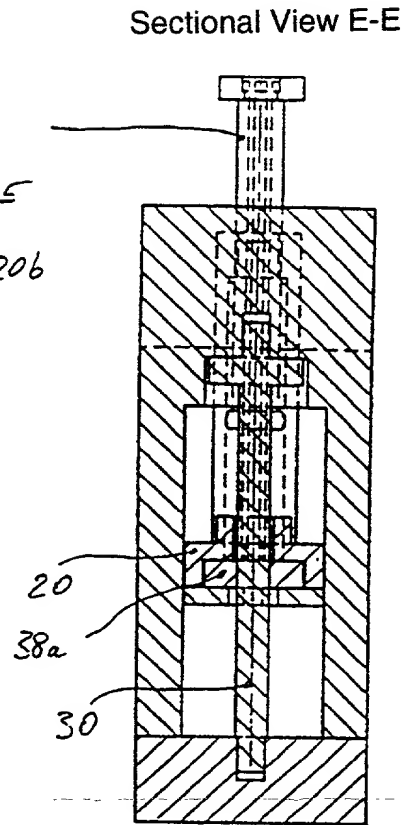


Fig. 21

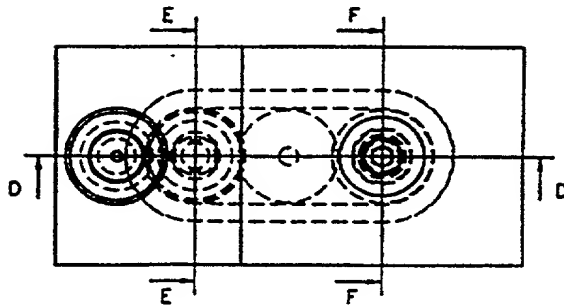


Fig. 19

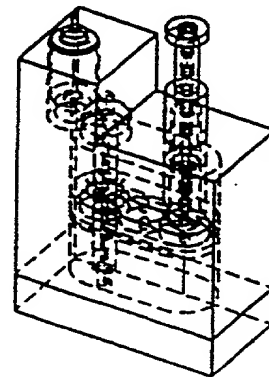


Fig. 22

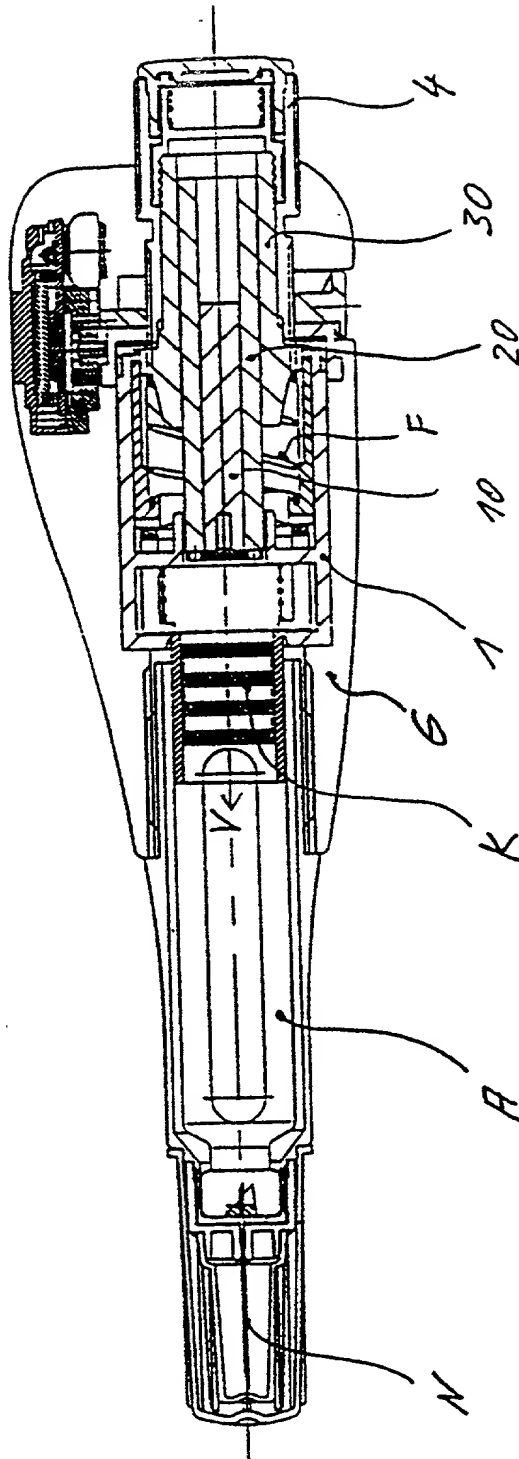


Fig. 23

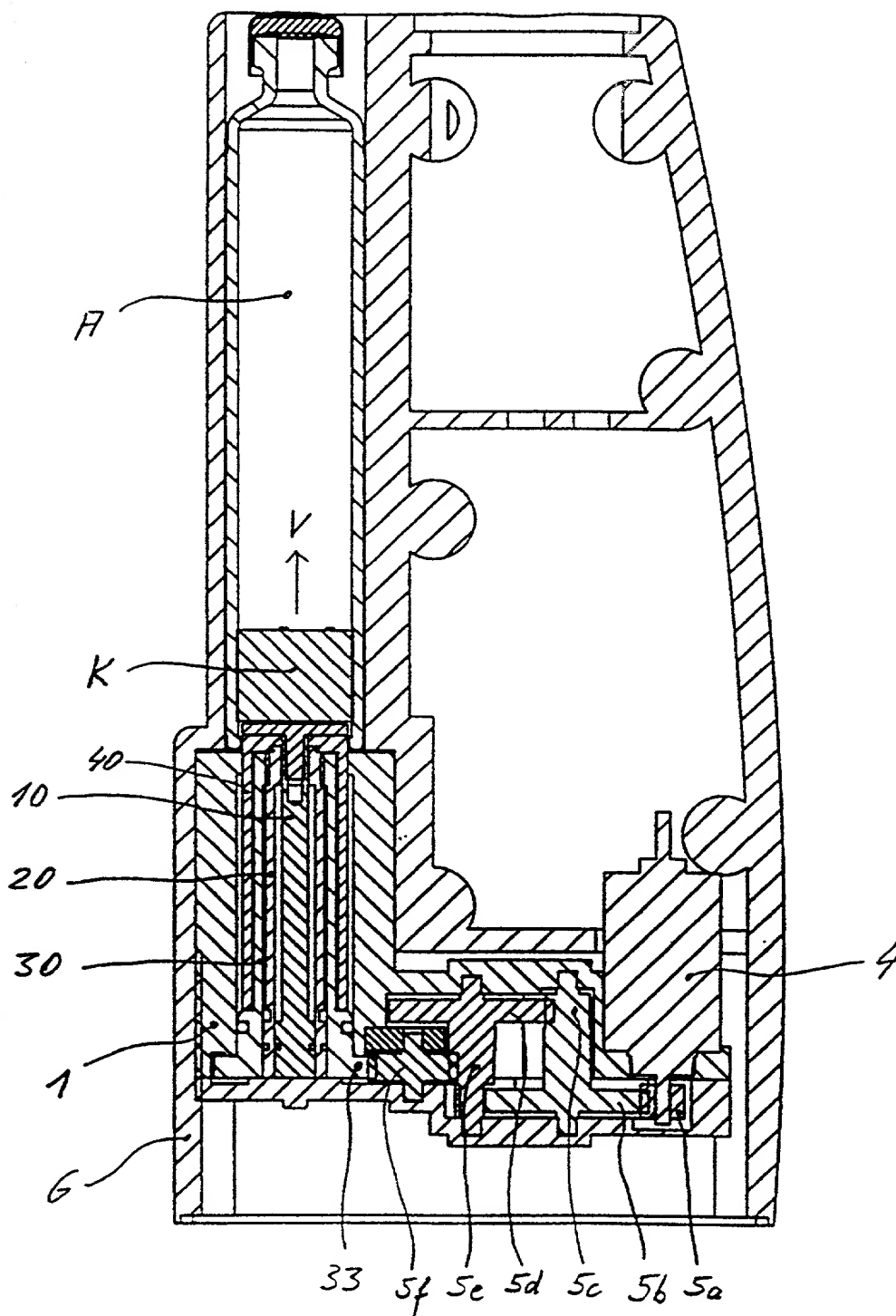


Fig. 24

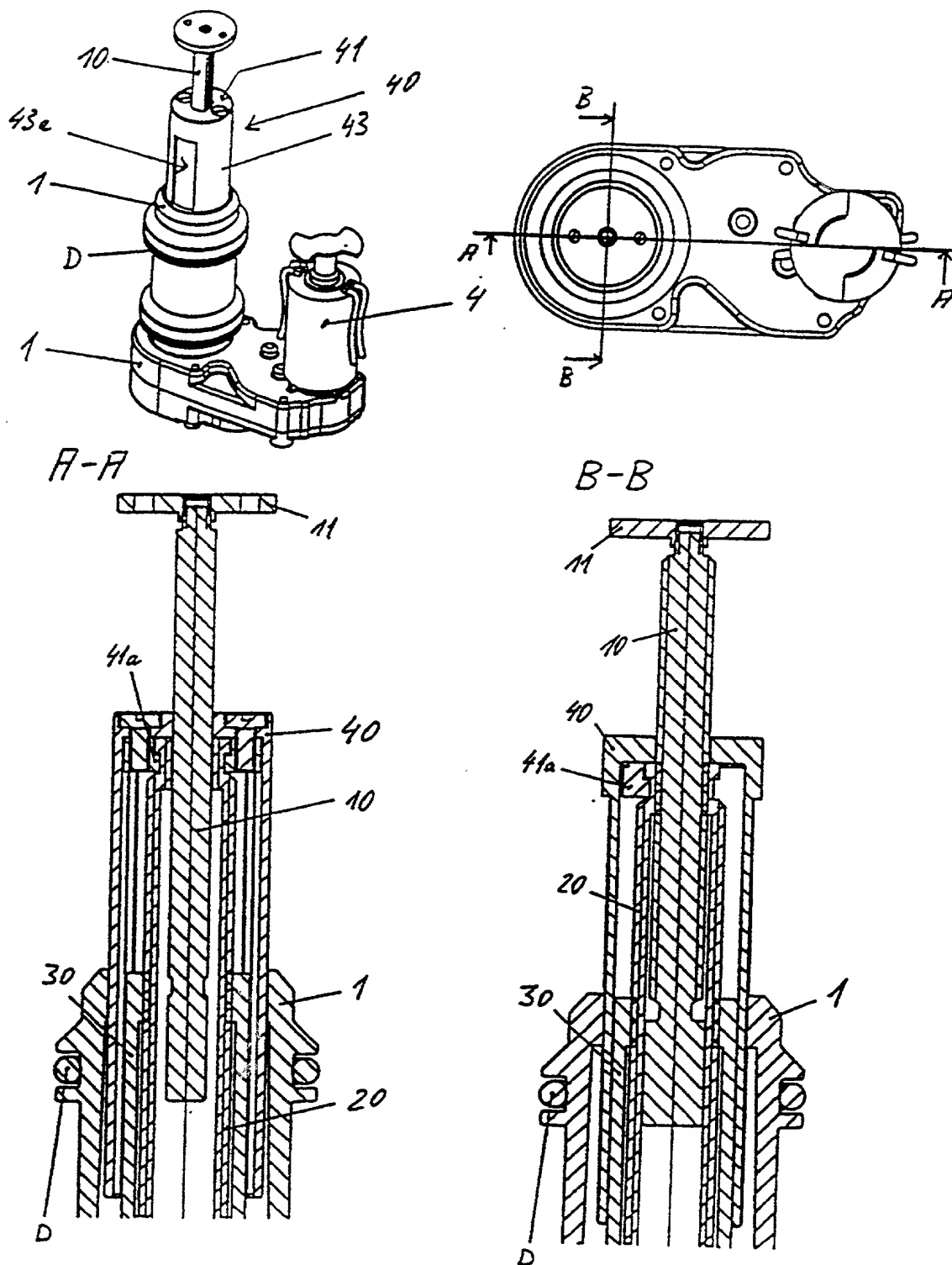


Fig. 25

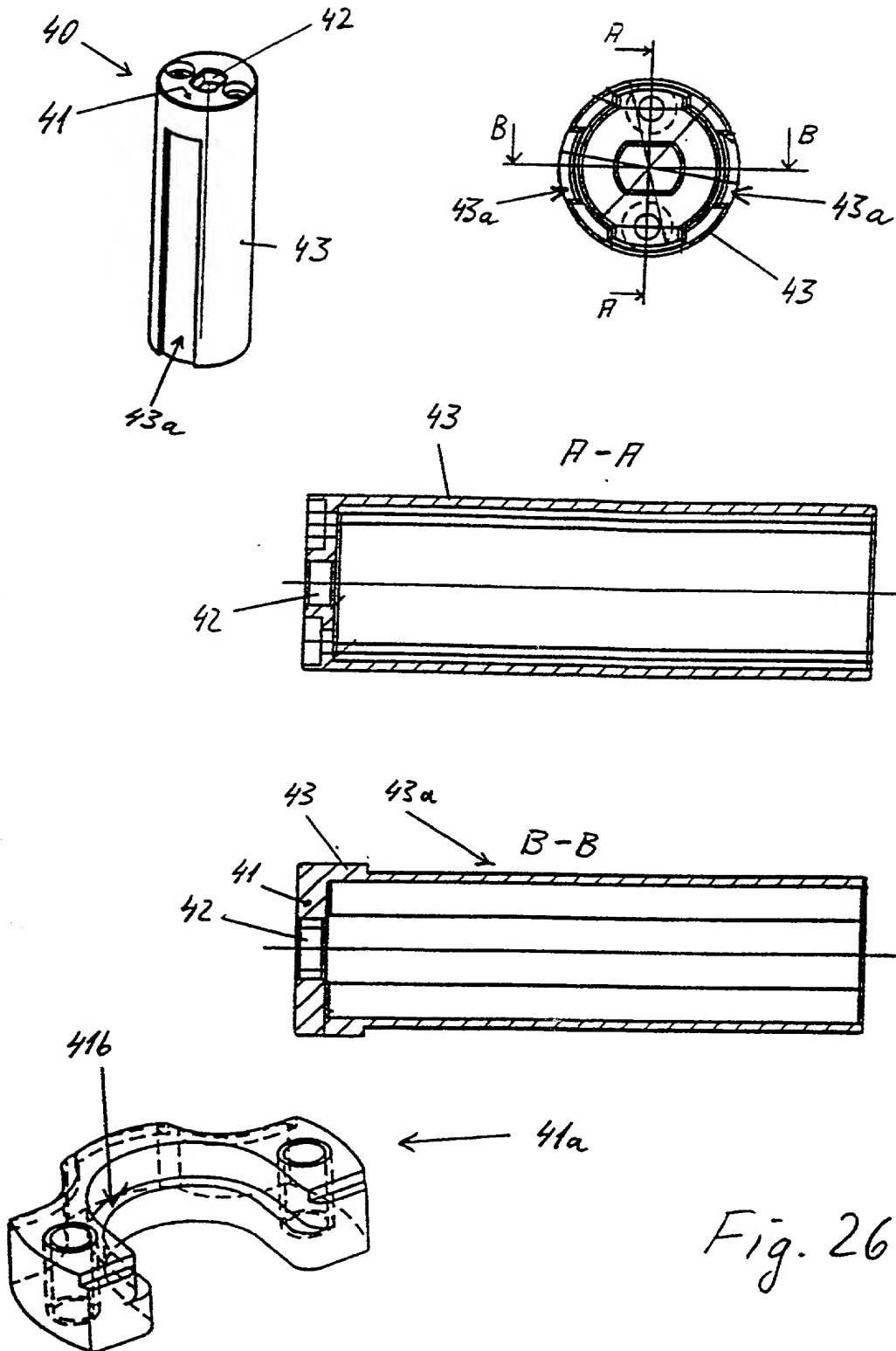


Fig. 26

**DECLARATION FOR PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **"Propelling Device for a Piston in a Container Containing a Liquid Medicament"**, the specification of which

is attached hereto.

was filed on October 22, 1999 as United States application number 09/403,431 and amended on (NA).

I do not know and do not believe that the invention was ever known or used in the United States before my or our invention thereof;

I do not know and do not believe that the invention was ever patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application;

I do not know and do not believe that the invention was in public use or on sale in the United States more than one year prior to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below, and I have also identified and listed below any foreign application(s) for patent or inventor's certificate, or PCT international application, having a filing date before that of the application(s) on which priority is claimed:

### FOREIGN APPLICATION(S)

Number	Country	day/month/year filed	Priority Claimed
PCT/CH98/00157	PCT	22 April 1998	23 April 1997
197 17 107.9	Germany	23 April 1997	NA

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any U.S. provisional application(s) listed below:

### U.S. PROVISIONAL APPLICATION(S)

Application Serial No.	Filing Date
NA	

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or under Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

### PRIORITY U.S. APPLICATION(S)

Application Serial No.	Filing Date	Status
NA		

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Ronald J. Brown (29,016), David E. Bruhn (36,762), David N. Fronek (25,678), Joseph F. Haag (42,612); Stuart R. Hemphill (28,084), Grant A. Johnson (42,696), Kenneth E. Levitt (39,747), Niall A. MacLeod (41,963), Devan Padmanabhan (38,262), Gerald H. Sullivan (37,243), Jon F. Tuttle (25,713), and Lance L. Vietzke (36,708).

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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